

SOLUBILITY OF CALCIUM PHOSPHATE GLASSES AND GLASS CERAMIC MATERIALS IN WATER AND PHYSIOLOGICAL MEDIA

N. Yu. Mikhailenko,¹ E. E. Stroganova,^{1,2} and N. V. Buchilin¹

Translated from *Steklo i Keramika*, No. 4, pp. 51 – 57, April, 2013.

The behavior of silicon- and aluminum-containing calcium phosphate glasses and glass ceramic materials in water and physiological media is examined from the standpoint of their use as implantation material for bone endoprosthesis and implantology. The results of a determination of the solubility parameters in *in vitro* experiments as a function of the chemical composition and structural particulars of the material are presented. It is confirmed that their use in *in vivo* experiments is promising.

Key words: calcium phosphate glass, glass ceramic material, biomaterials, bone endoprosthesis, solubility.

Phosphate glasses are of interest from the stand point of developing special glassy materials (laser, dosimetric, uvio), protective coatings and others. A promising direction, which has been under intensive development since the 1980s, is associated with the development on the basis of calcium phosphate systems biocompatible and bioactive glassy, glass ceramic, composite materials for bone endoprostheses [1 – 6]. The revolutionary nature of these biomaterials is due to their capability to stimulate the restoration of damaged bone tissue. Their biocompatibility and bioactivity are based on the structural and chemical similarity of the material to the section of bone being replaced and the biochemical processes occurring on its surface with the participation of collagen, proteins, pectins and macrophages, which promote resorption of the material and regeneration of the live bone tissue. The optimal behavior of the bone substitute is considered to be gradual degradation with complete replacement by the newly formed natural bone.

Resorption of the implant, i.e., its gradual resorption in the body right up to complete degradation as a result of the action of physiological fluid, osteoclasts and macrophages, is largely determined by the chemical properties and hydrolytic stability of the implant material. In this connection, in developing implantation materials for bone endoprostheses a great deal of attention is given to determining the level of solubility and interaction of the material with water and physiological media, finding the pathways for regulating solubility in a quite wide range in order to combine in time the processes leading to the resorption of the implant and osteogenesis of the bone tissue.

In the present article we present the results of research on the solubility *in vitro* of a number of calcium phosphate biomaterials for bone endoprosthesis — glass, glass ceramic materials and porous structures.

EXPERIMENTAL PROCEDURE

Chemically pure and analytically pure reagents were used as the initial materials for obtaining biomaterials: calcium carbonate, orthophosphoric acid (85% solution), silicon, aluminum, titanium and zirconium oxides and boric acid. The glasses were synthesized in an electric laboratory furnace at temperatures 1200 – 1400°C with 15 – 30 min soaking and subsequent output onto a metal plate. To obtain powder the glass was comminuted in a disk grinder and fractions with the required dispersity were extracted.

The glass ceramic materials with different types of structure were obtained: a) by casting glass technology (nonporous materials), b) by sintering of fine glass powder in the presence of disperse, fibrous and granulated consumable additives (materials with uniform or porous structure) and c) by the immiscible liquids method (porous granules). The granulometric composition of the glasses during the synthesis of porous materials was changed in the range 20 – 450 µm. Sintering and crystallization of the materials were conducted in an electric laboratory furnace in the temperature interval 900 – 950°C.

To determine the behavior of the materials in water media the powders or massive samples were boiled in distilled water for 1 h or held in artificial plasma in a thermostat at 37°C with the ratio material : medium = 1 : 100. The level of solubility was characterized the follow parameters: losses (or increment) of the material mass, change of the pH of the me-

¹ D. I. Mendeleev Russian Chemical Technology University, Moscow, Russia.

² E-mail: lab411@mail.ru.

dium and concentration of calcium ion in solution. The mass losses were determined by weighing the samples before and after treatment in water medium, the pH of the solutions and the yield of calcium ions by measuring the potential of glass and calcium electrodes in standard and experimental solutions in an I 160 M laboratory ionometer.

CALCIUM PHOSPHATE GLASSES, MODIFIED WITH SILICON OR ALUMINUM OXIDES

In the present work, three-component aluminum- and silicon-containing calcium phosphate glasses with molar ratio $\text{CaO}/\text{P}_2\text{O}_5 = 1.1$ and molar content of Al_2O_3 or SiO_2 from 2.5 to 20% (Table 1). The choice of these glasses is dictated by well-known tenets about the glass-forming power and hydrolytic stability of phosphate glasses.

Most phosphate glasses are chemically unstable. This is due to the structural particulars of the main structural element of the glasses — phosphorus-oxygen octahedron with one double and three ordinary bonds (one π -bond and three σ -bonds), and the structural particulars of the extended phosphorus-oxygen motif comprised of these tetrahedra. The character of the structural phosphorus-oxygen motif is determined by, first and foremost, the molar ratio of the sum of the modifying oxides to the binary calcium-phosphate glasses — ratio $R = \text{CaO}/\text{P}_2\text{O}_5$. For $R < 1$ a three-dimensional ultraphosphate glassy structure with a large number of hydrolytic unstable branch points, which are centers of chemical destruction of the material under the action of water media, easily formed in the material. Thus, binary ultraphosphate glasses corrode even when stored in air [10]. These glasses are not prone toward crystallization with additional heat-treatment, and the synthesis of glass ceramic materials based on them is impeded.

For $R = 1$ (metaphosphate compositions) extended polymer chains, formed by phosphorus-oxygen tetrahedra with two oxygen bridge atoms, predominate in the glass structure. Such structures are characterized by stronger bonds in a tetrahedron and greater chemical stability and proneness toward crystallization with additional heat-treatment. For higher values of R , equal to 2 or 3, short phosphorus-oxygen chains characteristic for pyro- and orthophosphates form. Such structures are distinguished by low glass-forming power, and they are difficult to obtain in the glassy state at ordinary rates of cooling of the melt.

The three-component compositions taken for these studies (see Table 1) lie in the metaphosphate region of the phase diagram of the $\text{CaO}-\text{P}_2\text{O}_5$ system. Glasses in this region are low-melting, are well melted at temperatures to 1400°C , are characterized by gradual (prolonged) surface dissolution in water media, and in the presence of catalytic additives can crystallize with the formation of a glass ceramic structure [10].

The introduction of a third component into binary calcium phosphate glasses strongly affects their hydrolytic sta-

TABLE 1. Solubility of Three-Component Calcium Phosphate Glasses in Water (Boiling of Powders for 1 h)

System	Molar content, %		Mass losses, %	pH of medium
	Al_2O_3	SiO_2		
$\text{CaO}-\text{P}_2\text{O}_5-\text{Al}_2\text{O}_3$	2.5	—	1.53	5.3
	5.0	—	0.67	5.7
	7.5	—	0.47	6.0
$\text{CaO}-\text{P}_2\text{O}_5-\text{SiO}_2$	—	5.0	5.70	5.0
	—	10.0	13.50	4.8
	—	15.0	43.10	4.0
	—	20.0	79.80	3.5

bility, which depends on the nature of the cation introduced (see Table 1). Aluminum oxide increases glass stability in water media — an increase of its content from 2.5 to 7.5% decreases the mass losses during treatment in water by a factor 3. Conversely, silicon oxide decreases the resistivity of glasses very strongly, making them hydrolytically unstable so that in time they completely degrade in water.

The nonunique effect of the oxides studied on the hydrolytic stability of glasses is a consequence of the different position of the added ions in the phosphorus-oxygen framework of the glass. According to previous studies [10], the aluminum cation, occupying in the glass structure the position of a modifying ion, binds chains of phosphate tetrahedra, increasing the connectedness of the glass structure as a whole. Such structures, which are more polymerized than binary ones, are chemically more stable. Silicon manifests the properties of a glass former and becomes incorporated into anionic phosphorus-oxygen chains, forming a mixed phosphorus-oxygen framework. The presence of two different cations — phosphorus and silicon — weakens the bonds inside the structural chains, makes them more hydrolytic and degrades the stability of the glass in water.

Aside from the low hydrolytic stability the behavior of phosphate glasses in interaction with water media exhibits a number of particularities, which fundamentally distinguish them from silicate glasses. The main difference is that as a result of leaching and hydrolysis high-silica hydrolyzed layers, possessing protective properties and slowing the interaction to the point of completely stopping it, form on the surface of silicate glasses. Such layers do not form on the surface of phosphate glasses; the interaction continues in time and in the absence of special measures results in complete degradation of the material. The capability of phosphate glasses to undergo prolonged (long-time) dissolution at a rate determined by their chemical composition makes it possible to obtain on their basis biomaterials that can be gradually replaced by newly formed bone and be completely resorbed into the body.

Another feature of the dissolution of phosphate glasses is that as a result of not only cationic but also anionic compo-

TABLE 2. Solubility of Three-Component Calcium-Phosphate Glasses in Artificial Plasma (Samples Thermostated at 37°C)

System	Content, mol. %		Losses, 10 ² g/cm ² after treatment		pH of medium after treatment	
	Al ₂ O ₃	SiO ₂	7 days	21 days	7 days	21 days
CaO–P ₂ O ₅	–	–				
CaO–Al ₂ O ₃ –P ₂ O ₅	2.5	–	0.08	0.13	6.9	7.0
	5.0	–	0.10	0.32	7.0	6.9
	7.5	–	0.11	0.26	7.2	7.1
CaO–SiO ₂ –P ₂ O ₅	–	5.0	1.40	2.51	6.8	6.0
	–	7.5	0.91	1.11	6.9	6.9
	–	10.0	0.54	0.61	6.9	7.0

nents of glass transitioning into water the medium becomes acidic with a low pH. Significant deviations of the pH of a medium from neutral in the direction of elevated alkalinity as well as in the direction of acidity adversely affect the viability of living tissues and limit the possibility of using a material in direct contact with them. Rapid dissolution of calcium-silicon-phosphate glasses is accompanied by a strong drop of the pH of the medium, which becomes acidic. In the presence of calcium-aluminum-silicate glasses the drop in the pH of the medium is not so critical because of their greater hydrolytic stability (see Table 1).

On the whole the regularities that have been found remain in the study of the behavior of synthesized glasses in artificial plasma, simulating the physiological medium in the body. Under these conditions calcium-silicate-phosphate glasses are likewise less hydrolytically stable than calcium-aluminum-phosphate glasses, though the differences in the values of their solubility parameters are not so great (Table 2). It should be kept in mind that when glasses are treated in artificial plasma prolonged dissolution of the material (mass loss of the sample) occurs in parallel with the formation on the surface of the material of layers of amorphous calcium phosphate (mass increment of the sample), which in the body act as donors of calcium and phosphorus ions, which are necessary for new bone to grow. In addition, artificial plasma is a buffer, stabilizing the acid-base characteristics of the medium. As a result the parameters studied (mass loss, pH of the medium) in this case are a complex reflection of several physical-chemical processes, which can have opposite effects on these parameters.

In summary, the introduction of a third component into metacalcium-phosphate glasses — silicon or aluminum oxide — makes it possible to synthesize biomaterials with much different hydrolytic stability in water media, ranging from extremely fast degradation (calcium-silicon-phosphate compositions) to comparatively high resistivity (calcium-aluminum-phosphate compositions).

CALCIUM PHOSPHATE GLASS CERAMIC MATERIALS

Glass ceramic materials — biositals, characterized by greater strength — are more effective (compared with bioglasses) for fabricating implants or endoprostheses that in the body are subject to static or dynamic loads [11, 12]. The behavior of glass ceramic biomaterials in water media and in the body is subject to more complex laws compared with glasses, since it is determined by many factors — the type and chemical properties of crystallized phases, their content in crystallized material, the chemical composition and content of the residual glassy phase.

The crystallization properties of the calcium phosphate glasses studied are determined by the ratio $R = \text{CaO}/\text{P}_2\text{O}_5$. Glasses with ultraphosphate compositions are highly stable against crystallization. Glasses in the meta-, pyro- and ortho-phosphate regions of the phase diagram ($\text{CaO}/\text{P}_2\text{O}_5 > 0.7$) crystallize in the temperature range 700 – 1100°C with calcium meta- and/or pyrophosphates precipitating and form a large-crystalline structure, characteristic for spontaneous surface crystallization of the glass. Catalytic and modifying additives (titanium, zirconium and boron) introduced into the glasses promote the formation of a uniform, volume-crystallized glass ceramic structure, represented by crystals of calcium, titanium, zirconium and residual glass phase. The solubility of crystalline pyrophosphates is extremely low, so that the behavior of the materials in water media is determined mainly by an unstable residual glass phase.

In the crystallization process, the chemical composition of the residual glass phase is constantly changing as a result of a transition of a definite part of the components into the crystalline component of the material. The calculations performed and the experimental determination of the composition of the residual glass phase by means of local x-ray spectral analysis [13] show that on crystallization the contents of phosphorus oxide and aluminum oxide (or silicon oxide) in the glass phase increase as the content of calcium oxide decreases. Thus, the molar content of P_2O_5 can reach 65%⁴ with CaO content less than 35% ($\text{CaO}/\text{P}_2\text{O}_5 = 0.46$), while the content of the third component (Al_2O_3) can increase to 10% (the initial composition of the glass (%): 39.1 P_2O_5 , 43.5 CaO, 4.35 Al_2O_3 , 4.35 B_2O_3 , 4.35 ZrO_2 and 4.35 TiO_2). In other words, on crystallization of the glass the composition of the residual glass phase shifts into the ultraphosphate region and becomes enriched with components that do not participate in the construction of the crystalline phase — aluminum or silicon oxide.

The crystallization shift of the composition of the residual glass phase into the ultraphosphate region must be accompanied by a sharp increase of the solubility of the crystallized material, similarly to the phenomenon observed in study in the hydrolytic stability of calcium phosphate glass

⁴ Here and below the molar content of the components, unless otherwise stipulated.

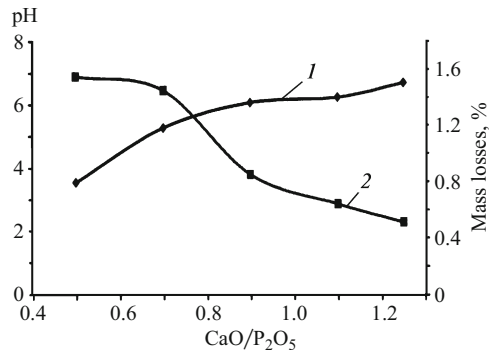


Fig. 1. Solubility of calcium-aluminum-phosphate glass ceramic materials in water versus the ratio $\text{CaO}/\text{P}_2\text{O}_5$ (powders thermostated at 37°C): 1) pH; 2) mass losses.

ceramic materials with different ratio $\text{CaO}/\text{P}_2\text{O}_5$ (Fig. 1). However, this effect has been observed experimentally only for calcium-silicon-phosphate glass ceramic materials (Table 3). In this case the degradation of the material in artificial plasma reaches high values and the pH of the medium drops catastrophically. The behavior of the calcium-aluminum-phosphate glass ceramic materials is significantly different: the specific mass losses are close to zero; the pH is stabilized at the level of a neutral medium and compared with the initial glass the hydrolytic stability is practically unchanged. The results obtained give a basis for assuming that the presence of a third component in the residual calcium phosphate that weakens (SiO_2) or strengthens (Al_2O_3) the phosphorus-oxygen motif of the glass phase has a predominating effect on the hydrolytic stability of the material. This factor is more important than a change in the ratio $\text{CaO}/\text{P}_2\text{O}_5$. In calcium-silicon-phosphate materials both factors, determining the solubility of the residual phase ($\text{CaO}/\text{P}_2\text{O}_5$ and the SiO_2 content), tend to lower its hydrolytic stability while in calcium-aluminum-phosphate materials these factors ($\text{CaO}/\text{P}_2\text{O}_5$ and the Al_2O_3 content) act in the opposite directions, which on the whole determines their much higher resistivity.

It is doubtful that calcium-silicon-phosphate glass ceramic materials will be used as implantation materials because of the strong increase in the acidity of the medium occurring when these materials undergo rapid dissolution. In the present work calcium-aluminum-phosphate glass ceramic materials were taken to develop biomaterials with a different type of structure.

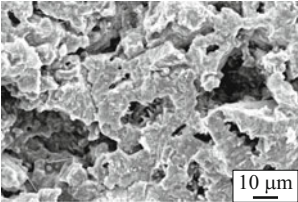
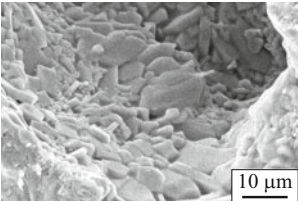
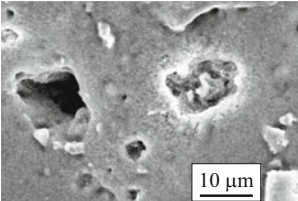
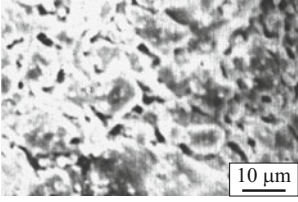
GLASS CERAMIC MATERIALS WITH DIFFERENT TYPES OF PORE STRUCTURE

In order to ensure a strong biochemical and mechanical bond between an implant and the bone tissue it is expedient to use porous glass ceramic materials with predominant pore size about $500\text{ }\mu\text{m}$. Glass ceramic materials with uniform porosity and channel or cellular pore structure as well as porous granulated materials based on crystallized calcium-alumi-

TABLE 3. Solubility of Glass Ceramic Materials in Artificial Plasma (Samples Thermostated at 37°C for 14 days)

System	Content, mol. %		Specific losses, 10^{-2} g/cm^2	pH of the medium
	Al_2O_3	SiO_2		
$\text{CaO}-\text{Al}_2\text{O}_3-\text{P}_2\text{O}_5$	2.5	—	0.03	7.2
	5.0	—	-0.32	7.2
	7.5	—	-0.33	7.2
$\text{CaO}-\text{SiO}_2-\text{P}_2\text{O}_5$	—	5.0	10.91	2.9
	—	7.5	12.93	3.6
	—	10.0	4.95	4.6

TABLE 4. Characteristics of Glass Ceramic Materials with Different Types of Pore Structure

No.	Material characteristics	Structure (SEM)
1	Glass particle size 40 – 450 μm . Consumable additive — starch. $P_{\text{open}} = 30 - 45\%$. Average pore size 60 – 150 μm	Uniform porosity 
2	Glass particle size 40 – 350 μm . Consumable additive — cotton filaments. $P_{\text{open}} = 40 - 60\%$. Channel pore size 150 – 500 μm	Channel porosity 
3	Glass particle size 20 – 40 μm . Consumable additive — paraffin granules. $P_{\text{open}} = 50 - 70\%$. Average pore size 500 – 2000 μm	Cellular porosity 
4	Glass particle size 40 – 80 μm . Consumable additive — gelatin. $P_{\text{open}} = 40 - 60\%$. Granule size 200 – 2500 μm	Porous granules 

num-phosphate compositions were studied in the present work (Table 4) [14, 15]. Blanks molded by different methods from calcium-aluminum-phosphate glass powder were heat-treated at $900 - 950^\circ\text{C}$, combining crystallization and sintering processes. The synthesized porous glass ceramic

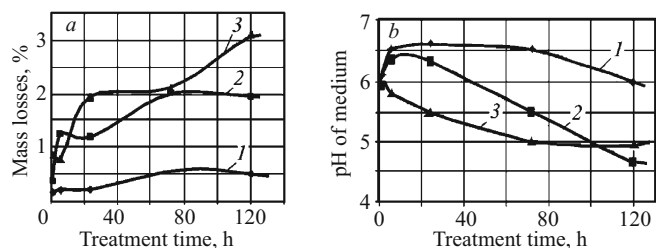


Fig. 2. Dissolution of porous calcium phosphate glass ceramic materials in water medium (thermostating of samples at 37°C): a) mass losses, %; b) pH of the medium; type of pore structure: 1) uniform; 2) channel; 3) cellular.

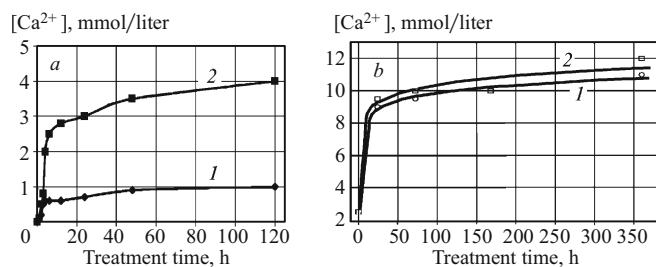


Fig. 3. Concentration of calcium ions in a solution of artificial plasma with thermostating of glass powders with particle size 20 μm (curve 1) and 40 μm (curve 2) (a) and materials with uniform structure and porosity 20 (curve 1) and 40% (curve 2) (b).

materials contained to 80% crystalline phase, represented by crystals of α - and β -Ca₂P₂O₇, TiP₂O₇ and ZrP₂O₇ and their solid solutions. The content of the residual glass phase was more than 20%.

The type of pore structure in the material has a strong effect on its hydrolytic stability and subsequent behavior inside the body. A transition from a uniform pore structure to channel and cellular structure is accompanied by an increase in the total porosity of the materials (see Table 4) and a significant increase of the specific contact area between the material and the surrounding medium. This accelerates the interaction between the material and the external medium, increases the mass loss and degradation rate of the material and changes the acid-base characteristics of the medium. Thus, a material with channel porosity and 120-h thermostating in water degrades four times more rapidly while a material with cellular structure six times more rapidly than material with an underdeveloped uniform pore structure under the same test conditions (Fig. 2). The highest rate of dissolution with developed porosity is fixed at the initial stages of the interaction — during soaking in water medium for up to 20 h. As the contact time with the medium increases the rate of degradation of the materials decreases, which could be associated with a decrease in the structure of the material of the amount of the unstable residual glass phase dissolving most actively at the initial stages of the interaction.

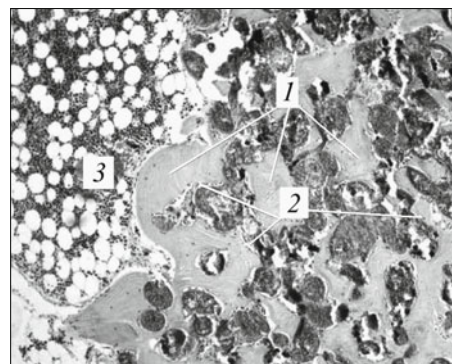


Fig. 4. Histological section of calcium phosphate glass ceramic biomaterial with channel pore structure, implanted into rabbit bone tissue, after 8 months of observation: 1) newly formed bone tissue; 2) osteocytes and osteoblasts; 3) bone marrow.

The role of the residual glass phase in the dissolution of porous materials can be illustrated using the results of the determination of the calcium ions in the solution of the artificial plasma with thermostating of calcium-aluminum-phosphate glass powder with dispersity 40 and 160 μm in it and massive samples of glass ceramic materials with uniform pore structure and porosity 20 and 40% (Fig. 3).

For minimum mass losses of the material with uniform porosity the concentration of calcium ions in a solution of artificial plasma is three times higher than in the presence of calcium-aluminum-phosphate glass, on the basis of which this material was obtained. The different rates of dissolution of glasses and materials based on them with the thermostating time increased above 1 day are related with the change in the composition of the residual glass phase.

When using highly porous materials the increase of the acidity (lowering of pH) of the surrounding medium during their intense dissolution can present a definite problem (Fig. 2). However, if the medium is continually renewed in the body this factor does not have an adverse effect on the surrounding tissue, which is indicated by tests of porous materials in *in vivo* experiments.

Implantation of the glass ceramic materials developed with porous structure of different types into chinchilla rabbit bone tissue at age 10 months to 1 yr showed that active growth of new bone tissues in the pore space of the implant is observed within 2 months after implantation. New bone tissue with osteocytes, osteoblasts and bone marrow was found in the channels of the material at 8 months of the experiment (Fig. 4).

CONCLUSIONS

The study of the solubility of glasses and glass ceramic materials in water and physiological media *in vitro* is a necessary step in the development of biomaterials based on them for bone endoprosthesis and implants and makes it possible to predict the behavior of these materials in the body.

The regularities found in the dissolution of calcium phosphate glasses and glass ceramic materials favor calcium-aluminum-phosphate sitals with channel pore structure. *In vivo* experiments with these materials attest to their efficacy as implantation materials in bone surgery.

This work was performed with the financial support of the RF Ministry of Education and Science under contract No. 11.G34.31.0027 "New functional possibilities of glasses and glass ceramics."

REFERENCES

1. P. D. Sarkisov, *Directed Crystallization of Glass — Base for Obtaining Multifunctional Glass Ceramic Materials* [in Russian], D. I. Mendeleev Russian Chemical Technology University, Moscow (1997).
2. M. Vallet-Regi, "Evolution of bioceramics within the field of biomaterials," *C.R. Chimie*, **13**, 174 – 185 (2010).
3. G. Georgiou and J. C. Knowles, "Glass reinforced hydroxyapatite for hard tissue surgery. Part 1: mechanical properties," *J. Biomater.*, **22**, 2811 – 2815 (2001).
4. A. Hoppe, N. S. Gldal, and A. R. Boccachini, "A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics," *J. Biomater.*, **32**, 2757 – 2744 (2011).
5. L. Hench, "Bioceramics," *J. Am. Ceram. Soc.*, **81**(7), 1705 – 1728 (1998).
6. L. L. Hench, I. D. Xynos, and G. M. Pollak, "Bioactive glasses for in situ tissue regeneration," *J. Biomater. Sci. Polim.*, **15**, 543 – 562 (2004).
7. J. R. Van Vaser, *Phosphorus and Its Compounds* [Russian translation], Inostr. Lit., Moscow (1962).
8. V. V. Tarasov, *Problems of Glass Physics* [in Russian], Stroiizdat, Moscow (1979).
9. B. K. Brow, "Review: the structure of simple phosphate glasses," *J. Non-Cryst. Solids*, **263 – 264**, 1 – 28 (2000).
10. N. Yu. Mikhailenko, P. D. Sarkisov, and E. E. Stroganova, "Effect of small additions of silicon, aluminum and boron oxides on the structure of calcium phosphate glasses," in: *Tarasov Lattice and New Problems of the Glassy State* [in Russian], RFO, Moscow (1999), pp. 38 – 41.
11. T. Kokubo, S. Ito, and M. Shigematsu, "Mechanical properties of a new type of apatite-containing glass-ceramics for prosthetic application," *J. Mater. Sci.*, **6**(20), 2001 – 2006 (1985).
12. W. Vogel, W. Holand, and K. J. Naumann, "Control of phase formation processes in glass-ceramics for medicine and technology," *Non-Cryst. Solids*, **129**(1 – 3), 152 – 162 (1991).
13. P. D. Sarkisov, N. Yu. Mikhailenko, E. E. Stroganov, et al., "Structure formation in porous calcium phosphate systems," *Dokl. Akad. Nauk*, **443**(5), 1 – 4.
14. P. D. Sarkisov, N. Yu. Mikhailenko, E. E. Stroganova, and N. V. Buchilin, "Glass-based porous materials," *Steklo Keram.*, No. 10, 13 – 16 (2008); P. D. Sarkisov, E. E. Stroganova, N. Yu. Mikhailenko, and N. V. Buchilin, "Glass-based porous materials," *Glass Ceram.*, **65**(9 – 10), 333 – 336 (2008).
15. P. D. Sarkisov, N. Yu. Mikhailenko, E. E. Stroganova, et al., "Porosity and solubility of bioactive calcium-phosphate glass ceramic materials for bone endoprosthesis," *Steklo Keram.*, No. 5, 40 – 45 (2012).